

# Tuberculosis from a Clinician's Perspective

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Epidemiology and Laboratory Priorities

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# Tuberculosis from a Clinician's Perspective

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- Epidemiology
- Transmission and Pathogenesis
- Diagnosis and Treatment of Tuberculosis
- Diagnosis and Treatment Latent TB Infection (LTBI)
- Laboratory Priorities-A Clinician's Perspective

# The Global Resurgence of Tuberculosis

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“The microbe is nothing:  
the terrain, everything.”

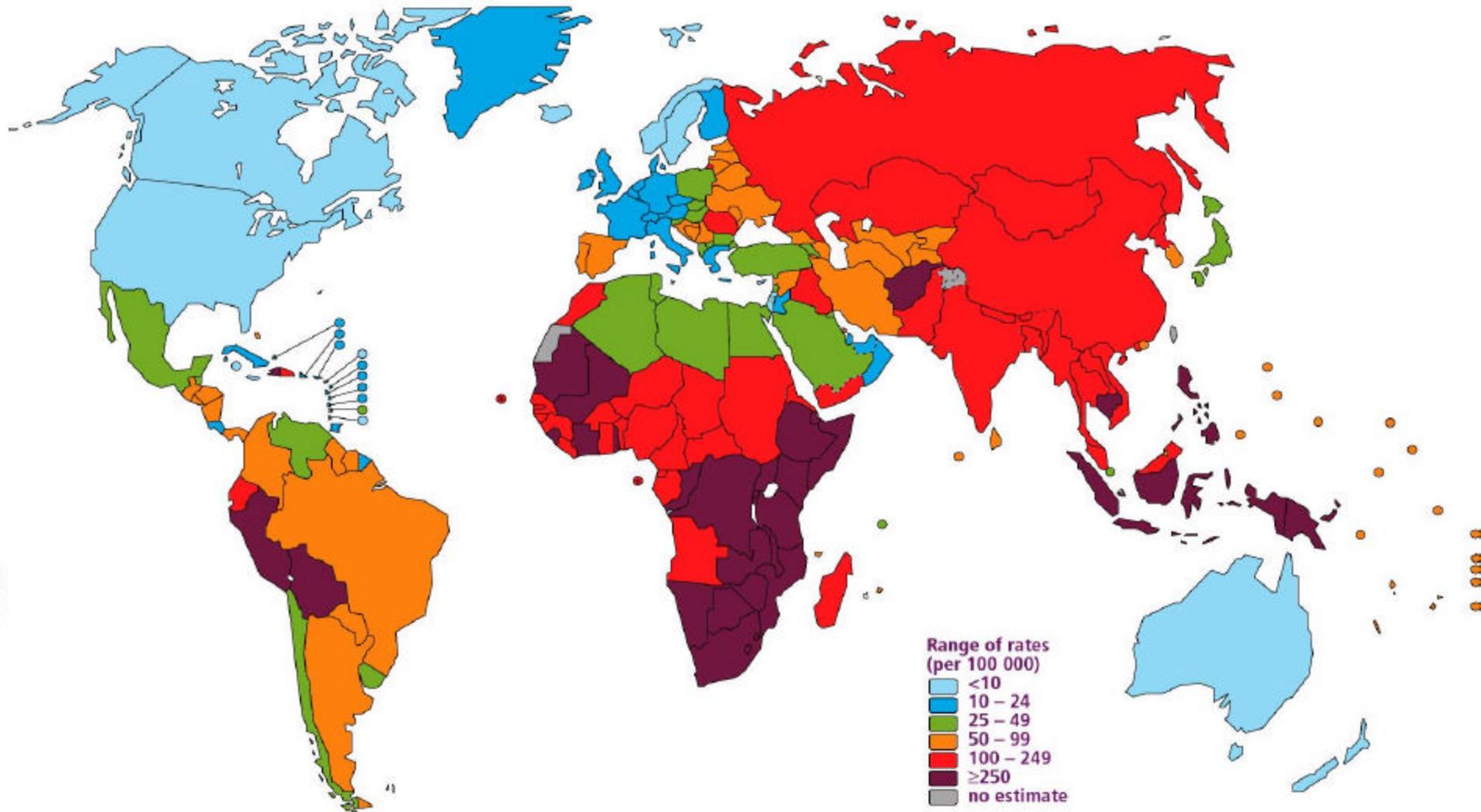
– L. Pasteur, 1822-1895

# Magnitude of Tuberculosis

Prevalence of infection	2 billion
Annual number of new cases	8 million
Annual case rate	60.6/100,000
Tuberculosis deaths*	2 million
% preventable deaths	26

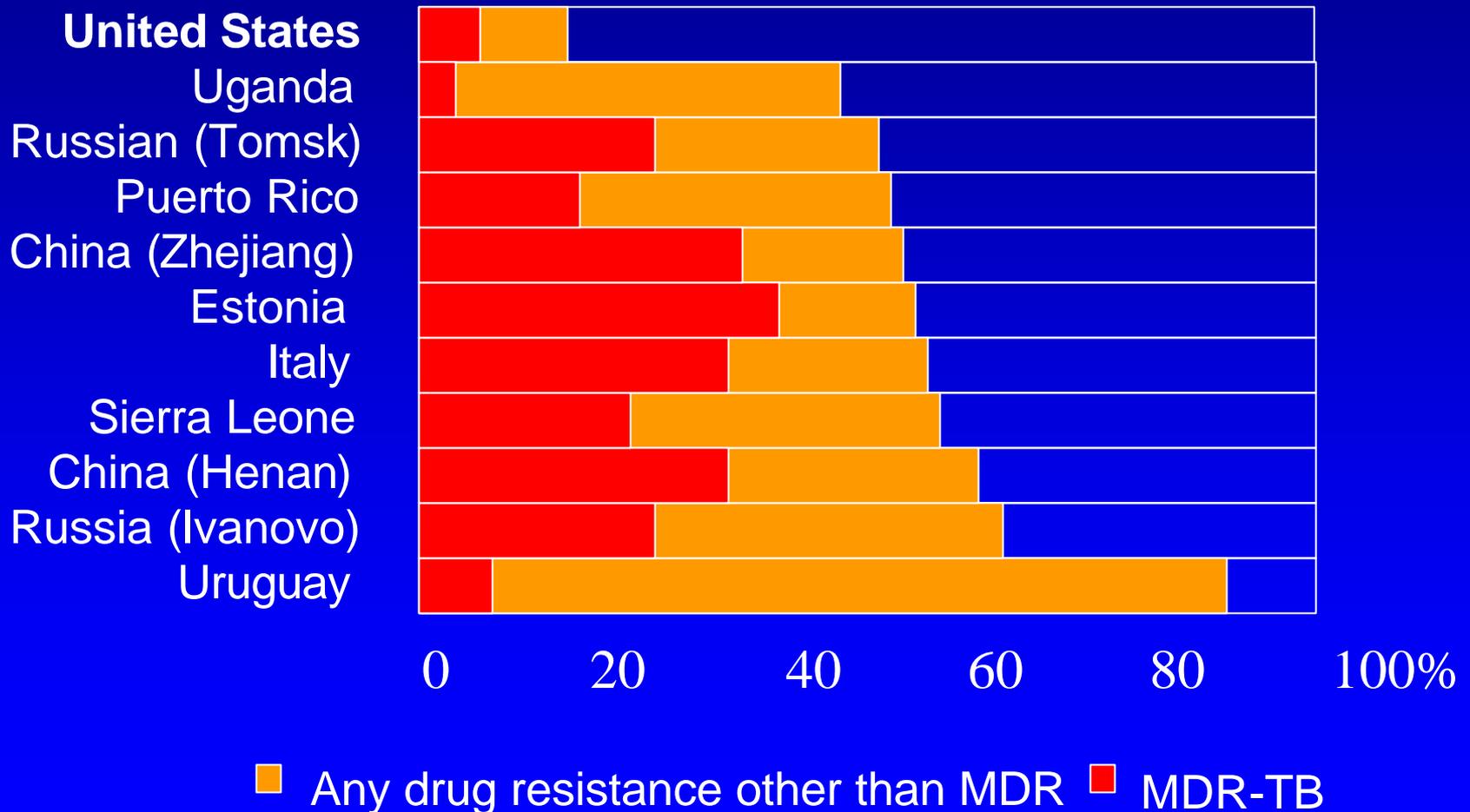
\*Does not include TB/HIV deaths

# Estimated TB Incidence Rates, 1997

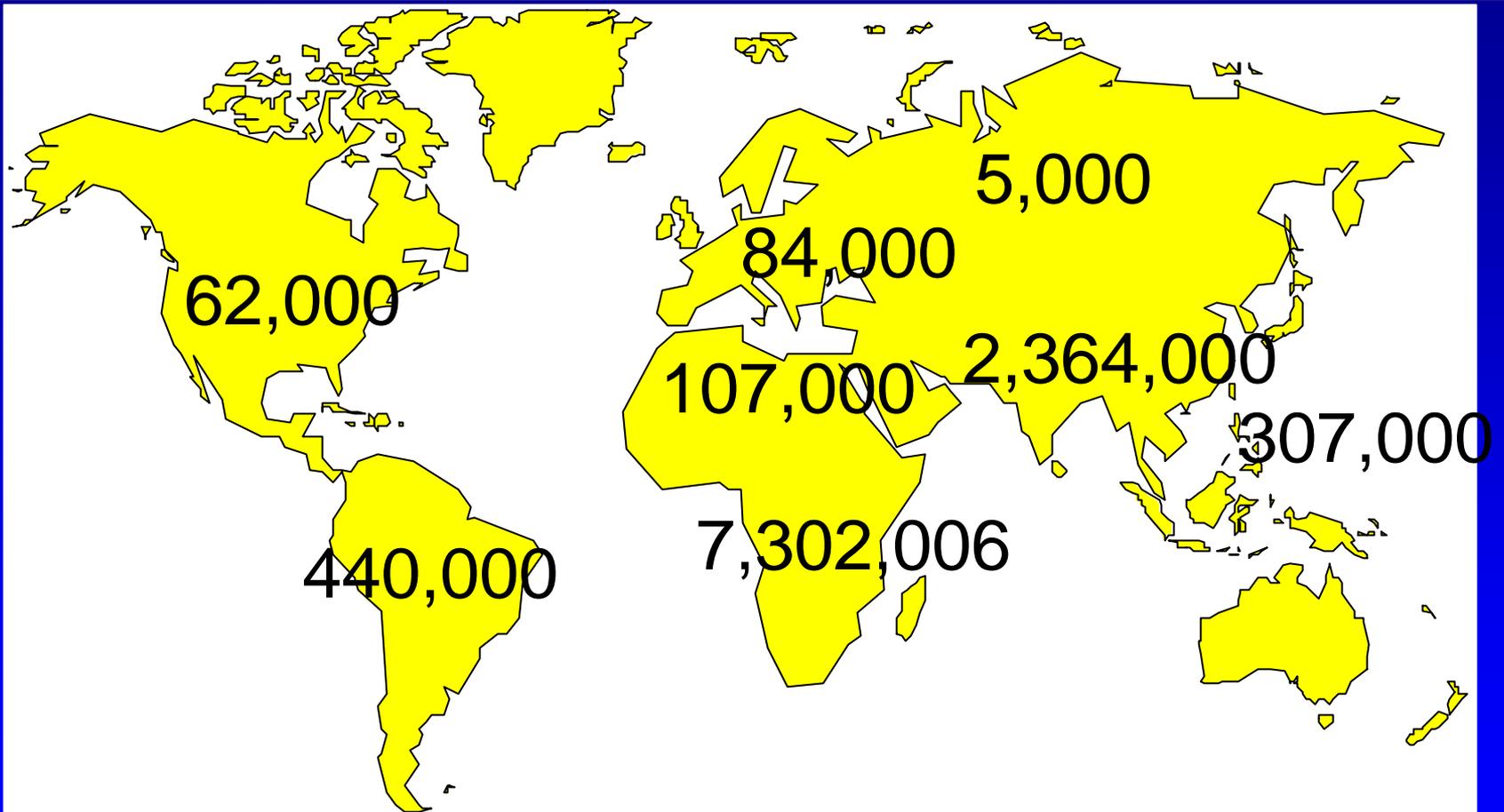


# WHO Global Project

## Prevalence of MDR-TB in Previously Treated

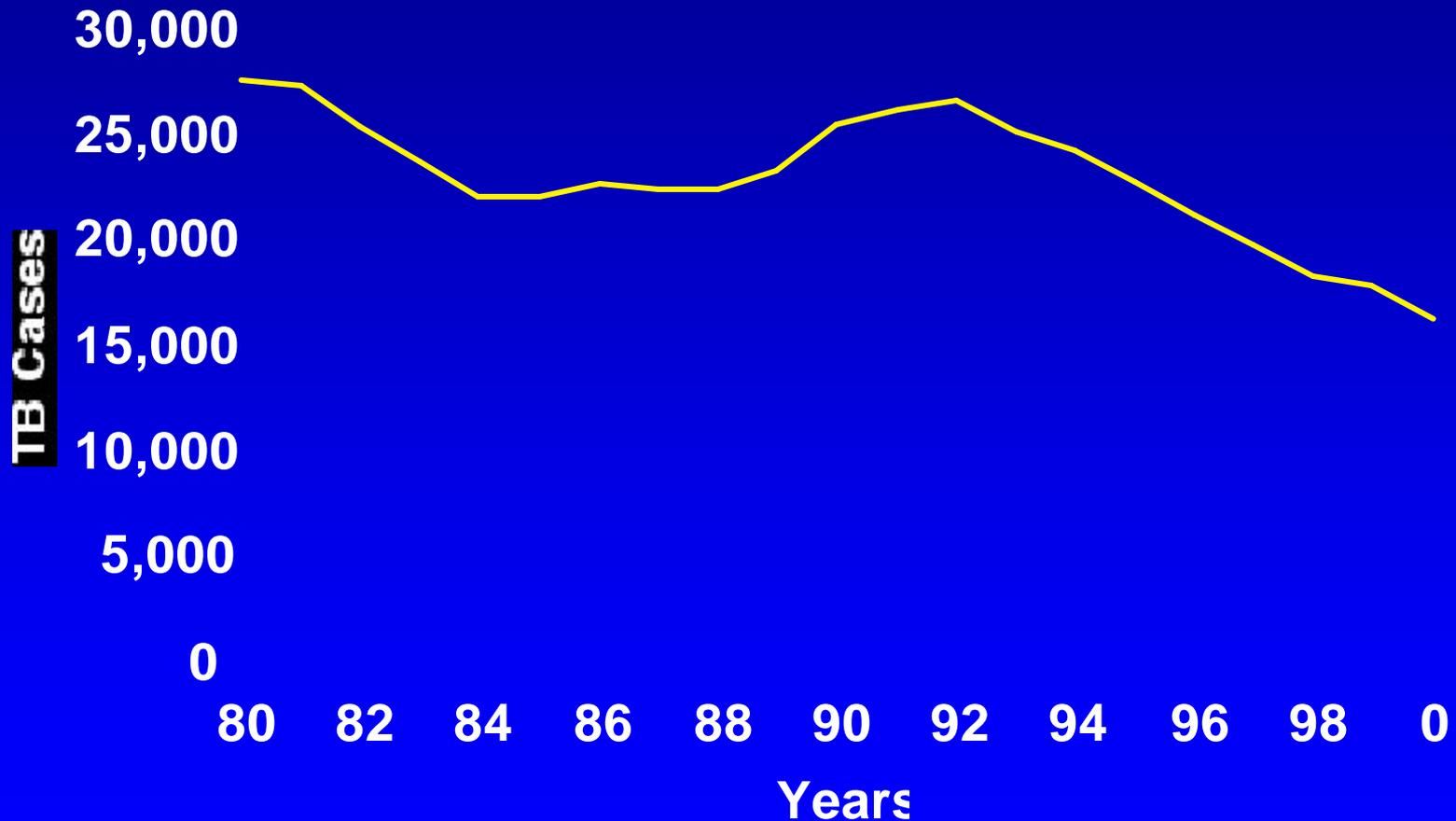


# Global Distribution Of HIV/MTB



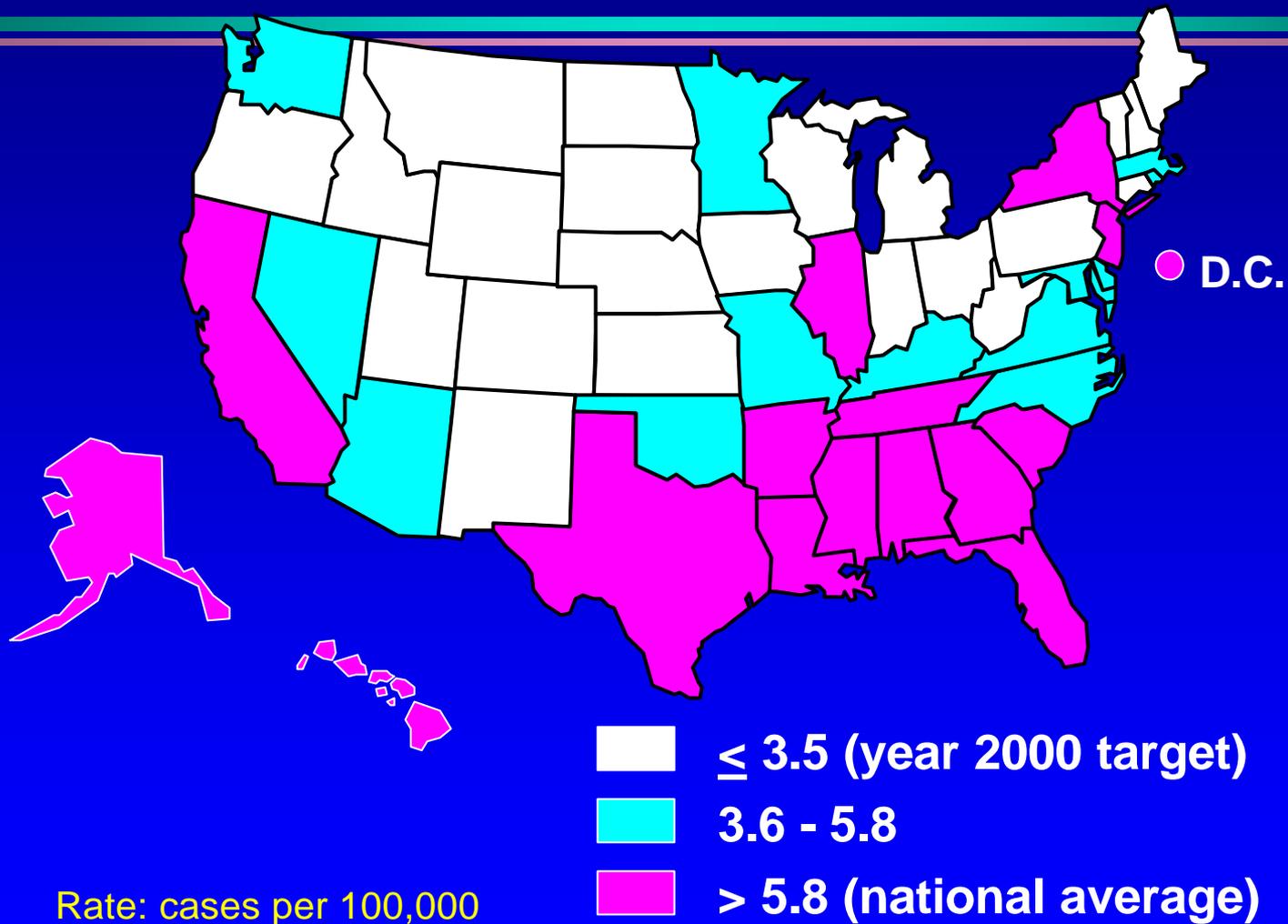
GLOBAL TOTAL: 10.7 MILLION

# Tuberculosis Cases in the U.S. 1980-2000



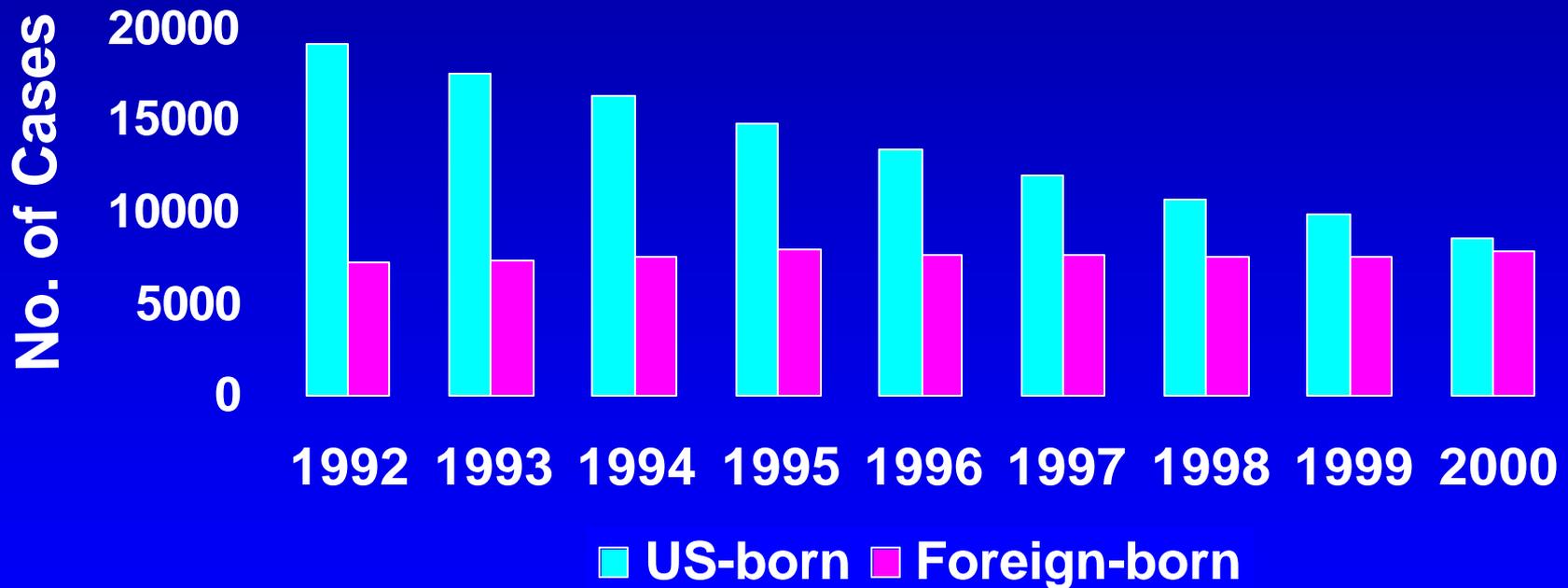
Source: CDC

# TB Case Rates in the U.S., 2000



# Number of TB Cases

US-born vs. Foreign-born , 1992-2000



# TB Cases In The United States

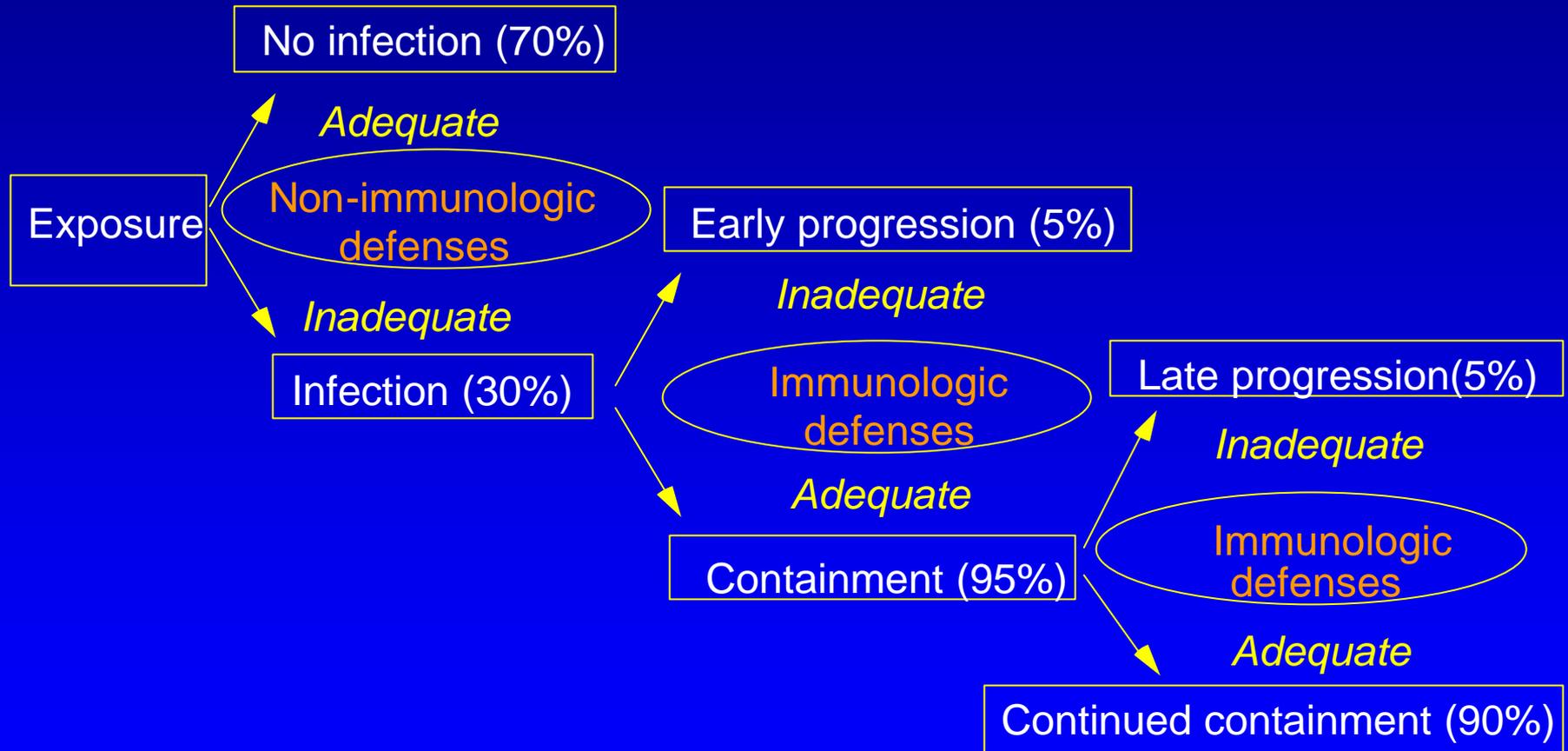
## Age 24-44, by HIV Status, 1998

<u>Reporting Area</u>	<u>Total Cases</u>	<u>Cases with HIV Status</u>		<u>% HIV +</u>
		<u>No.</u>	<u>%</u>	
Alabama	107	85	79.4	12.9
Florida	544	457	84.0	46.8
Georgia	228	174	76.3	29.9
Louisiana	132	103	78.0	18.4
Maryland	112	92	82.1	28.3
New York City	652	548	84.0	39.6
Oregon	71	60	84.5	13.3

Source: CDC



# Transmission and Pathogenesis of TB



# Diagnosis of Tuberculosis

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- 400 B.C. Clinical observation and deduction - Hippocrates
- 1761 Percussion - Anenbrugger
- 1819 Auscultation - Laennec
- 1882 Microscopic examination and culture - Koch
- 1895 Xrays - Rontgen

# Sensitivity and Specificity

## A Laboratory Perspective

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- Sensitivity - The percentage of patients with the disease who have a positive test
- Specificity - The percentage of patients without disease who have a negative test

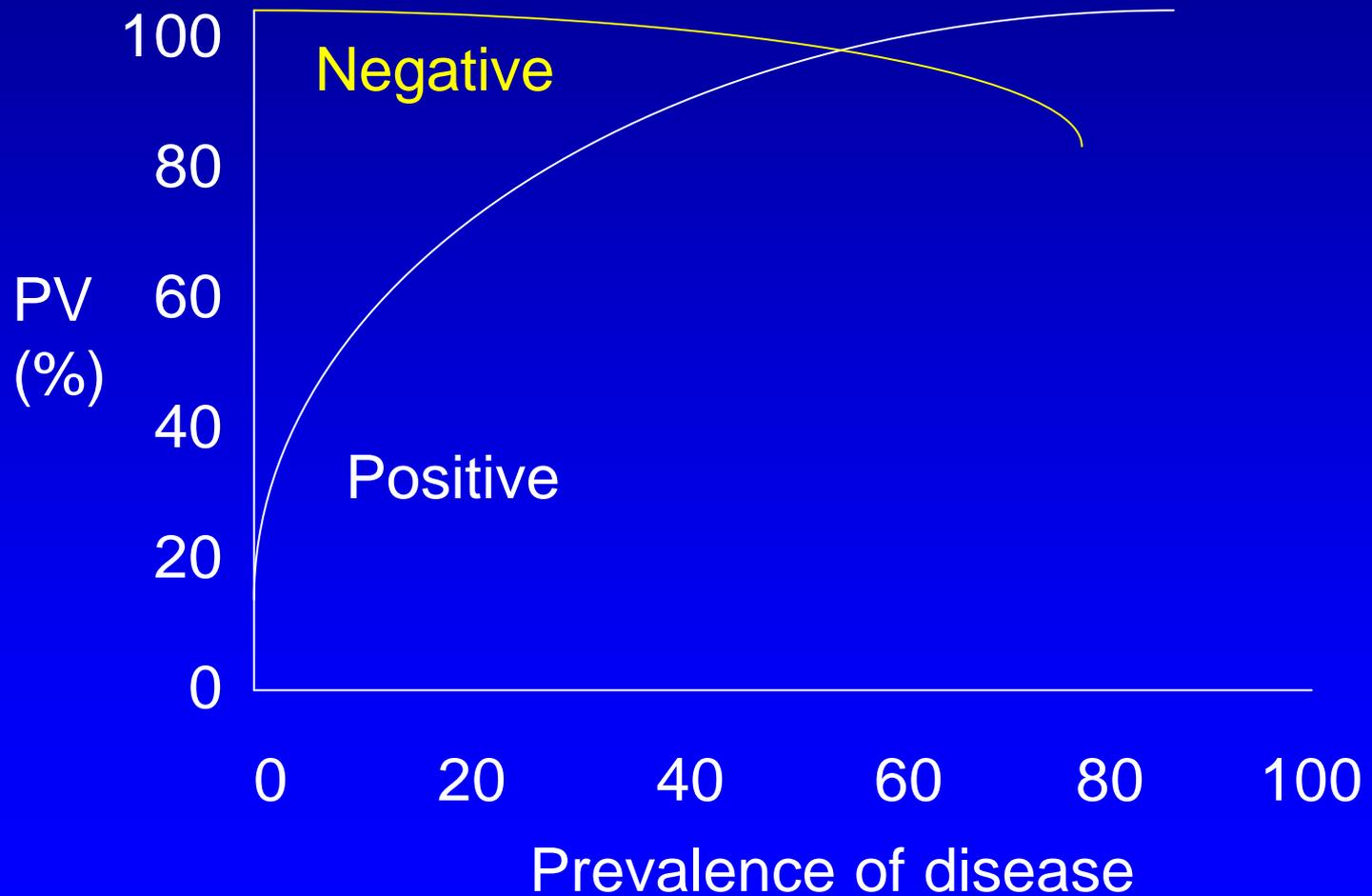
# Predictive Values

## A Clinician's Perspective

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- Positive predictive value (PPV) - The percentage of patients with a positive test who have the disease
- Negative predictive value (NPV) - The percentage of patients with a negative test who do not have the disease

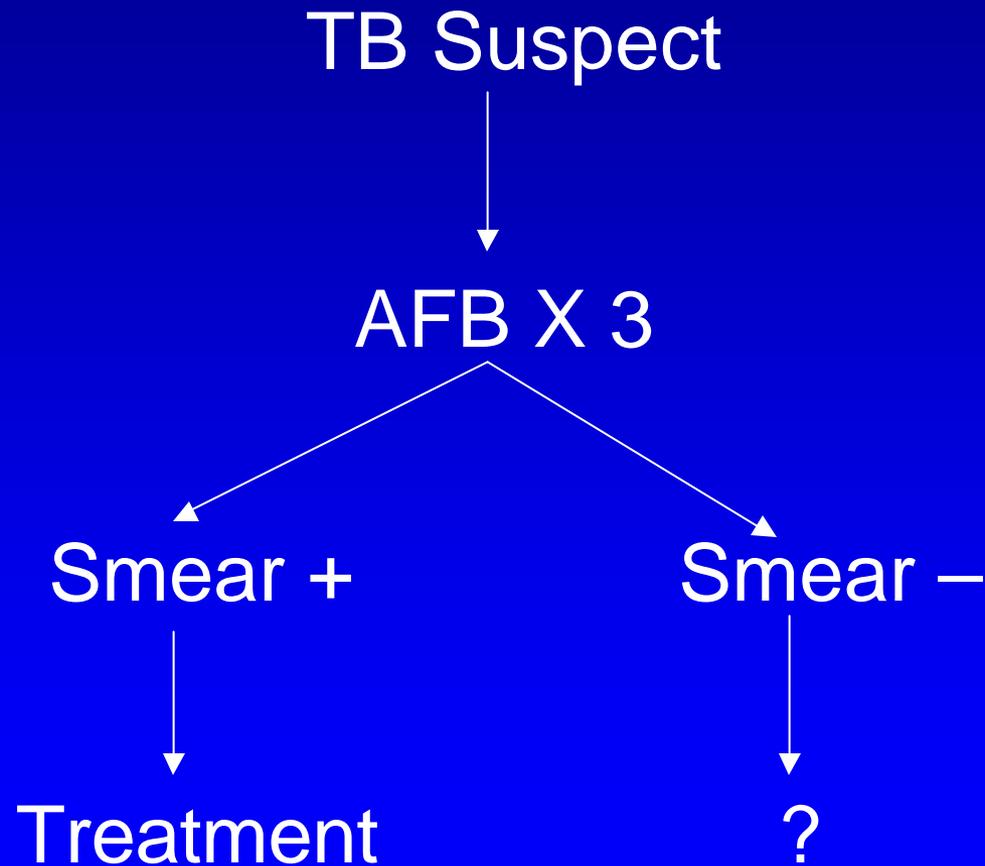
# Prevalence of Disease vs. Predictive Value



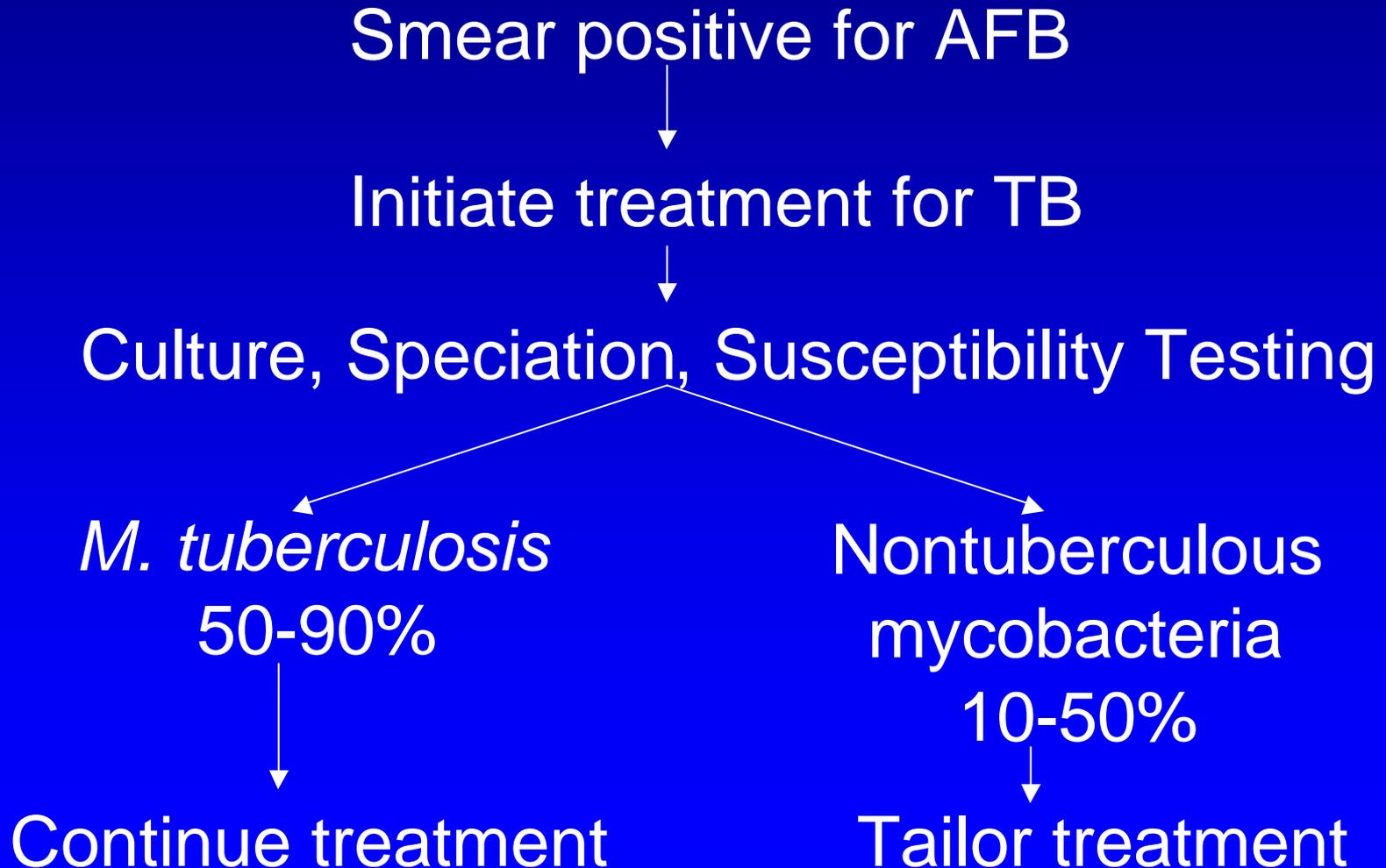
# TB or Not TB?



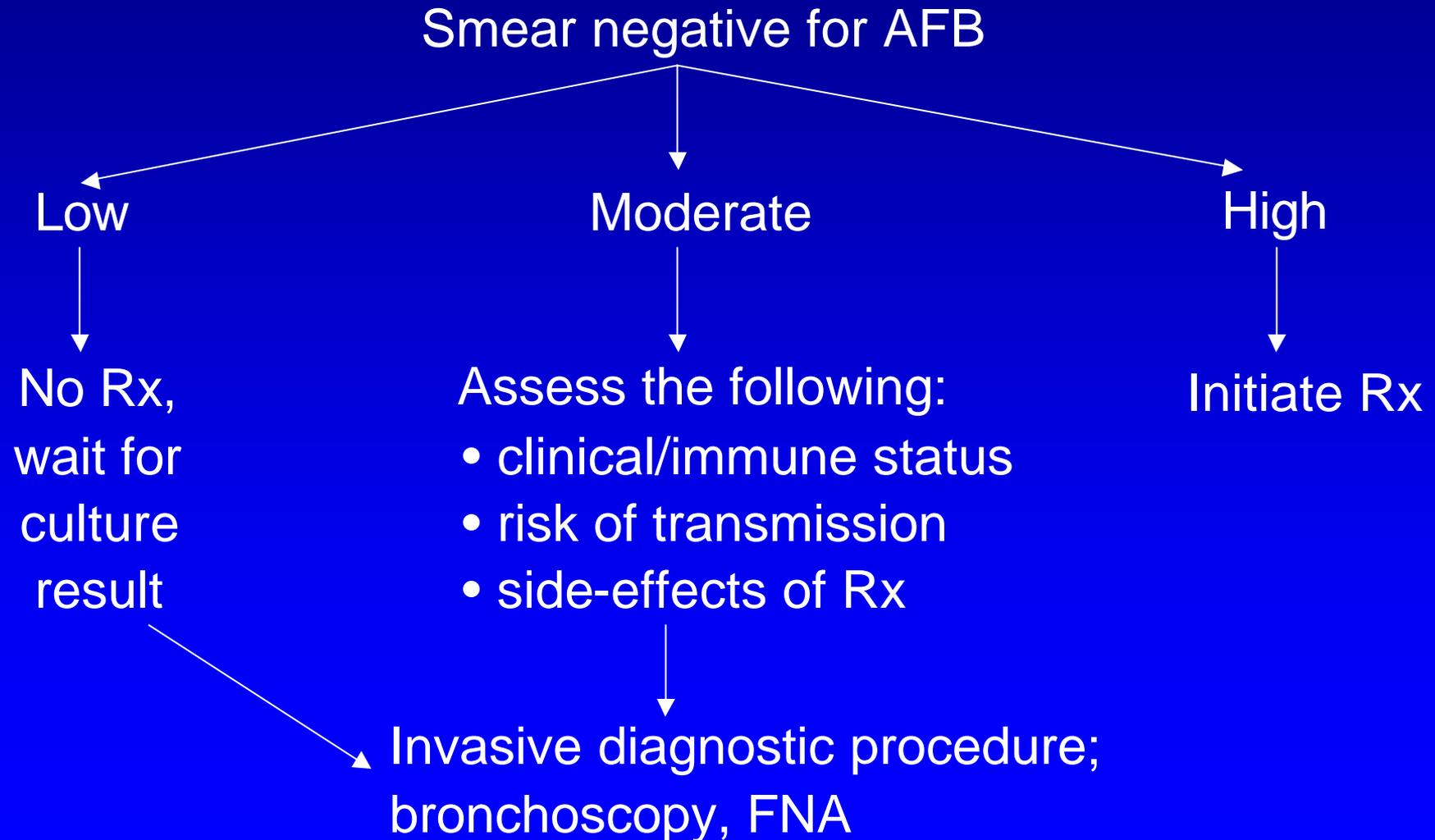
# Diagnostic Work-Up of TB Suspect



# Predictive Value of a Positive AFB Smear

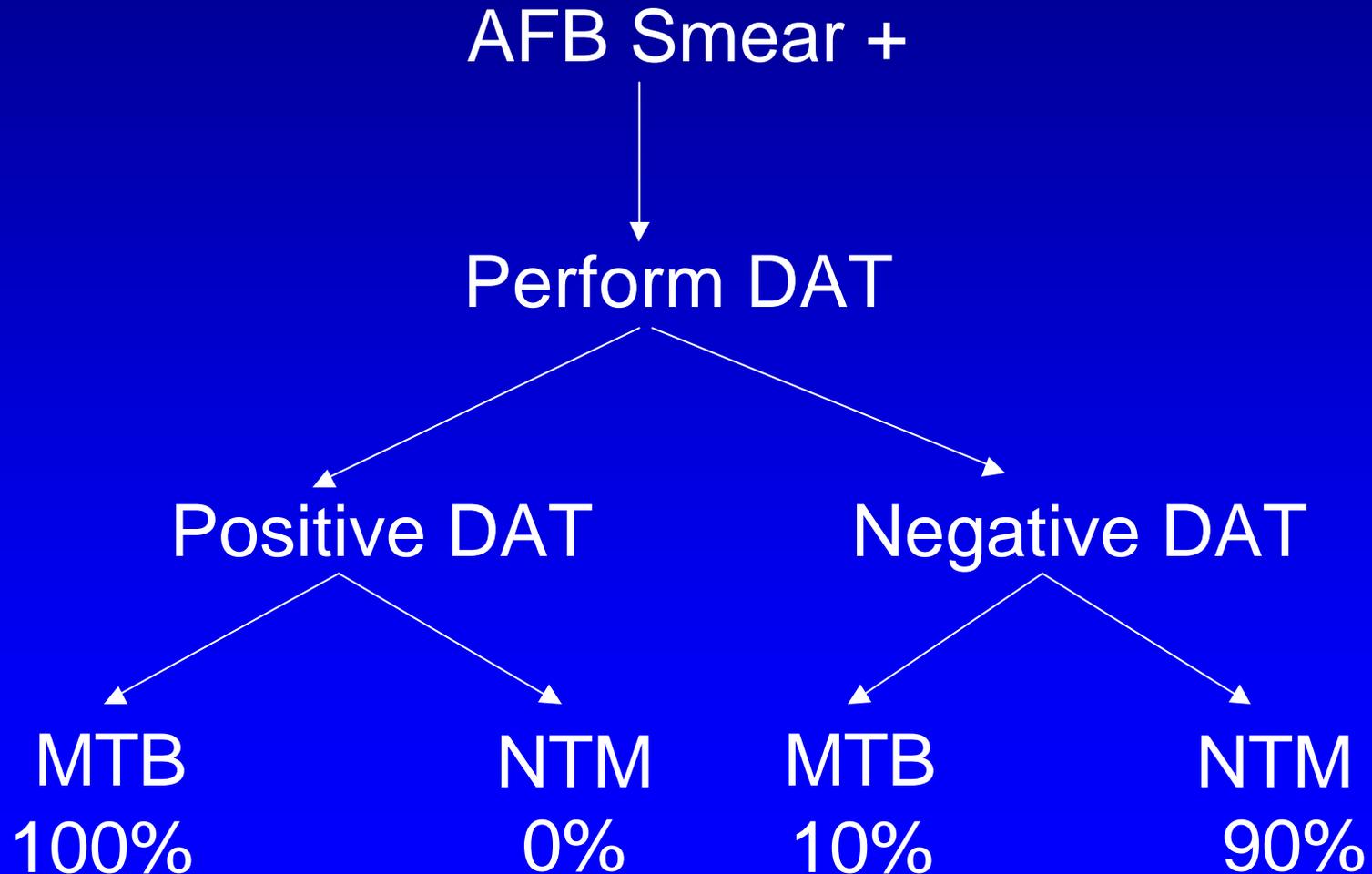


# Clinical Decision Making with Negative AFB Smears



# Direct Amplification Tests

## Smear Positive Specimens



# Diagnosis of Tuberculosis

## Role of Clinical Suspicion

- Prospective multicenter trial
  - » 7 sites (6 in U.S. and 1 in Switzerland)
- 338 TB suspects were enrolled
- Patients were stratified by clinical investigators to be at:
  - » Low (= 25%)
  - » Intermediate (26-75%)
  - » High (>75%) risk of TB

# Diagnosis of Tuberculosis

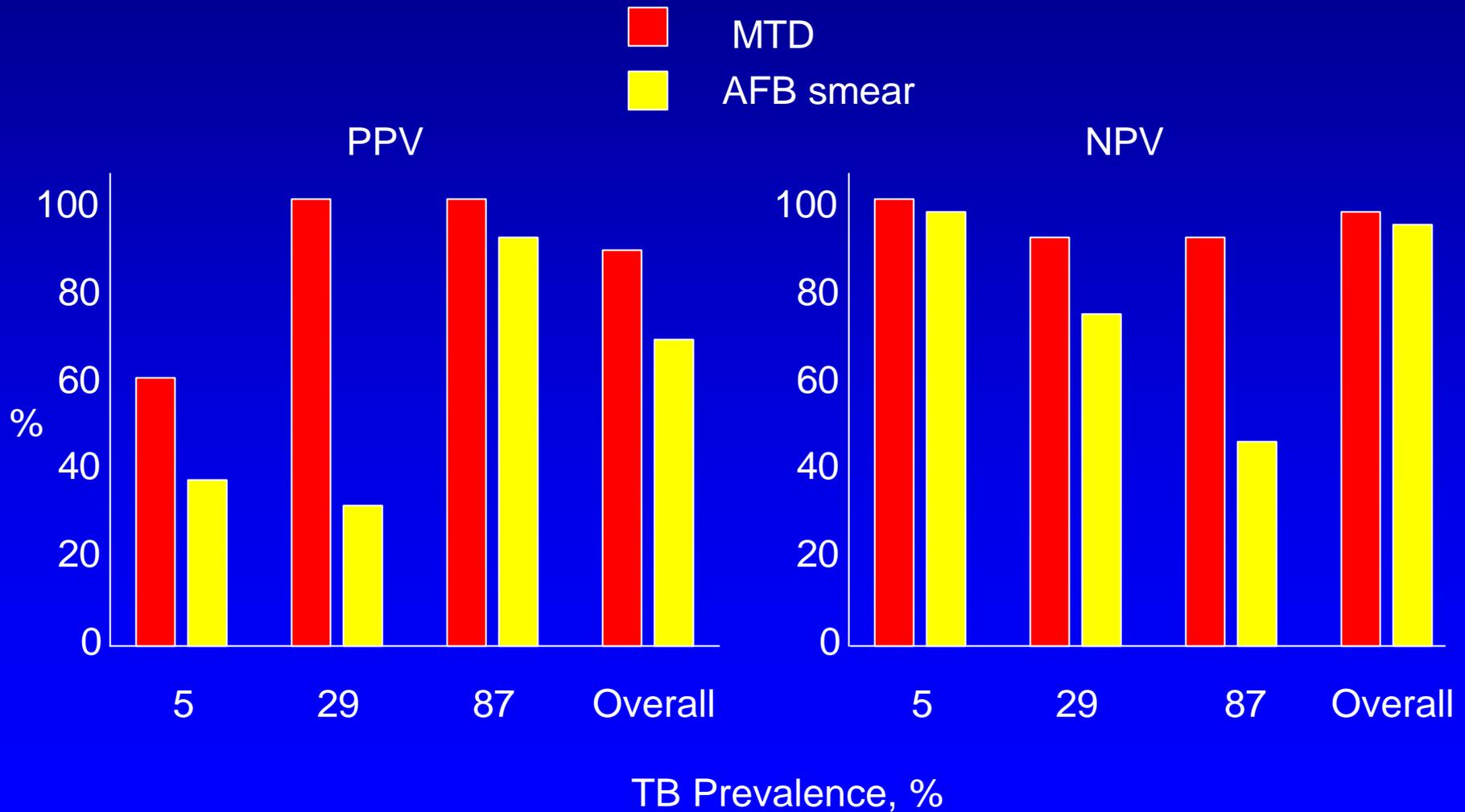
## Role of Clinical Suspicion

- Among 338 suspects, 72 had TB
  - 45 (63%) had = 2 positive cultures
  - 20 (28%) had one positive culture
  - 7 (10%) had not positive cultures

	<i>Low</i> <i>(n= 224)</i>	<i>Intermediate</i> <i>(n=68)</i>	<i>High</i> <i>(n=46)</i>
Prevalence of TB	5%	29%	87%
Started on drugs	11%	49%	98%

# Diagnosis of Tuberculosis

## Role of Clinical Suspicion



# Treatment of Tuberculosis

## Unscientific and Probably Ineffective

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- Wolf's liver boiled in wine
- Flesh of a she-ass with broth
- Smoke of dried cow dung
- Elephant's blood
- Woman's milk
- Mice boiled in salt and oil

# Treatment of Tuberculosis

## San Francisco General Hospital



# Treatment of Tuberculosis

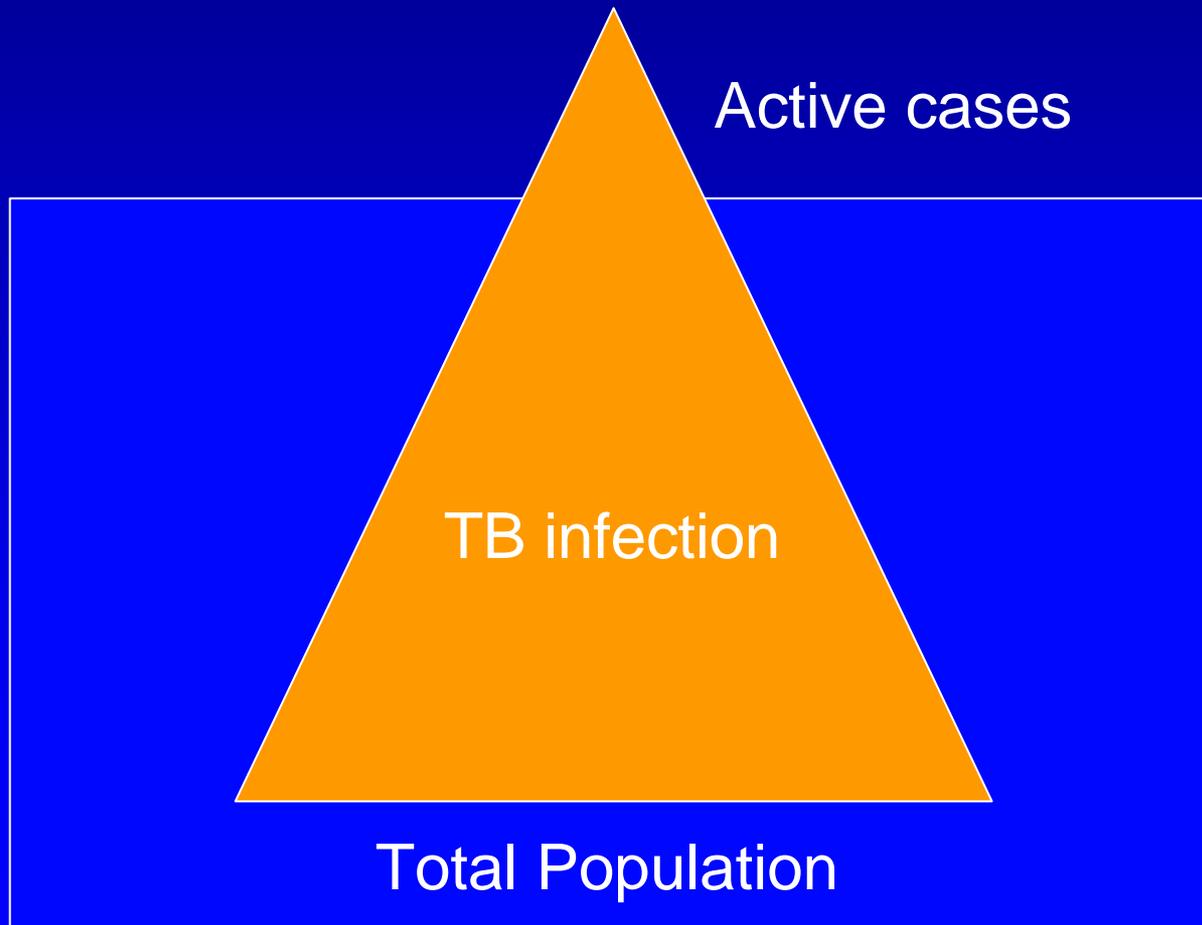
## Standard Regimen



\*Streptomycin may be substituted

# Tuberculosis

## Tip of the Iceberg



# Tuberculin Skin Testing

## Mantoux Method



# Quanti-FERON-TB<sup>®</sup> Test

Collect  
blood



Dispense blood into wells



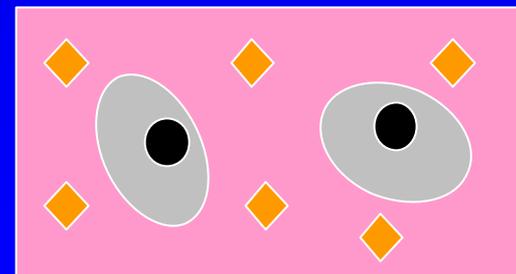
Add simulation  
antigens to blood



Nil  
antigen    Hu  
PPD    Av  
PPD    Rec  
antigens    Mitogen  
control



Specific T cells  
respond and produce  
gamma-interferon



→ ELISA

# Quanti-FERON-TB<sup>®</sup> Test

## Impact of BCG Vaccination

	% Agreement			<i>kappa</i>
	<i>Overall</i>	<i>TST+</i>	<i>TST-</i>	
Total Population	84.7	64.8	90.2	0.55
Unvaccinated	88.1	64.5	91.3	0.50
Unk. Vaccination	82.2	72.1	88.0	0.61
BCG Vaccinated	70.1	61.5	81.8	0.41

# Quanti-FERON-TB<sup>®</sup> Test

## Discordance: +TST, -QFT

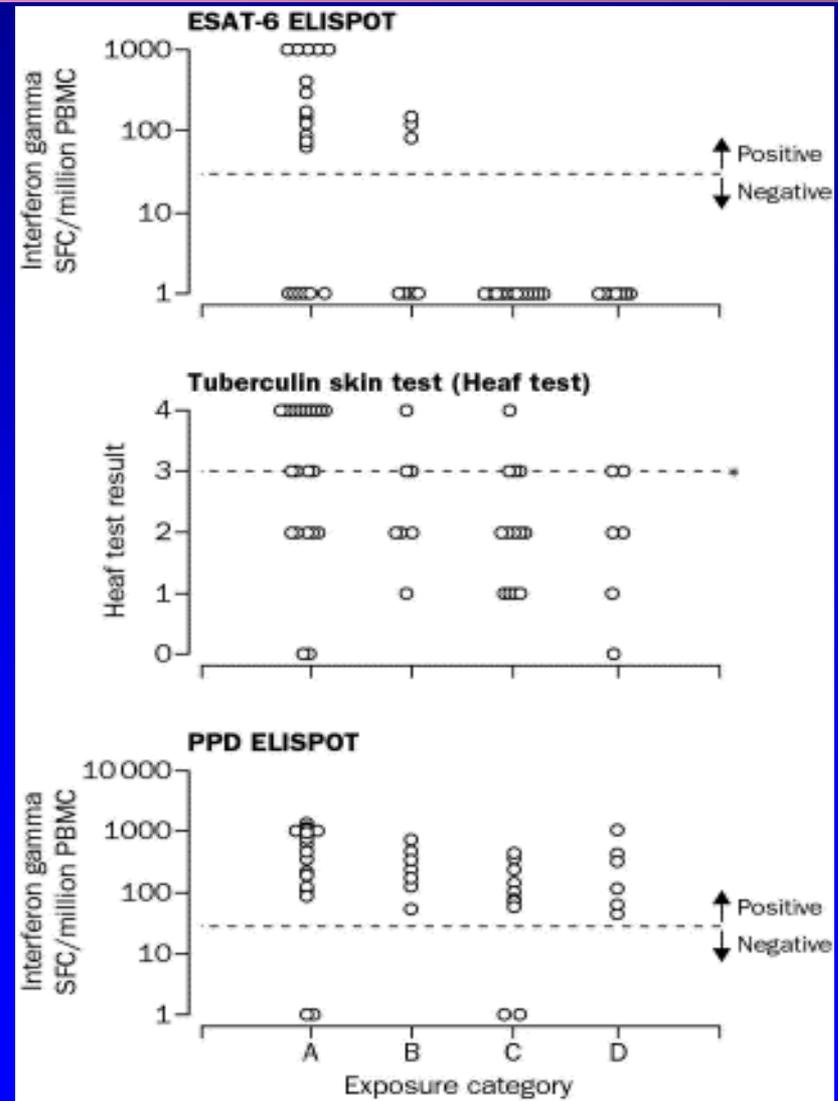
<i>Variable</i>	<i>Category</i>	<i>Relative Risk</i>	<i>P-value</i>
Race	White	1.0	
	Hispanic	1.24	0.63
	Black	1.69	0.15
	Asian	2.33	0.03
	Other	0.61	0.66
History of BCG	None	1.0	
	Unknown	2.49	0.03
	Vaccinated	6.92	0.00
MAC by QFT	No	1.0	
	Yes	2.64	0.008

# ESAT-6 ELISPOT Assay

## Contacts Stratified by Exposure

- 50 healthy contacts with well-defined degrees of exposure
- ESAT-6 correlated with degree of exposure
- ESAT-6 was not correlated with BCG status

Lalvani, et al. Lancet 2001;357:2017-21



# Treatment of LTBI

## Drug Regimens

<i>Regimen</i>	<i>Duration (months)</i>	<i>Interval</i>
Isoniazid	9	Daily Twice-wkly
Isoniazid	6	Daily Twice-wkly
Rifampin-PZA	2 2-3	Daily Twice-wkly
Rifampin	4	Daily

# Laboratory Priorities

## A Clinician's Perspective

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- Services offered - The more the merrier
- Turn around time - The quicker the better
- Communication - It's a good thing
- Costs?

# Laboratory Priorities

## A Clinician's Perspective

<i>Test</i>	<i>Positive characteristics</i>	<i>Negative characteristics</i>
Smear	Rapid Inexpensive + Infectiousness	Not sensitive
Culture	Definitive diagnosis	Slow
Susceptibility tests	Identifies drug resist.	Slow
Amplification tests	Rapid Sensitive and specific	Expensive – Infectiousness

# Drug Susceptibility Testing Priorities

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- Isoniazid
  - » Low and high concentrations?
- Rifampin
- Pyrazinamide
- Ethambutol
- ?Streptomycin?

# Communication

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- Communication is essential for patient care
- Speed of reporting results must be balanced against the reporting of accurate results
- In suspected cross-contamination, the clinician should be informed immediately

# A Clinician' Laboratory Wish List

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- Diagnosis and treatment of TB
  - » Rapid identification-species specific
  - » Correlate with infectiousness of patient
  - » Rapid drug susceptibility testing
  - » Determine response to therapy
- Diagnosis and treatment of LTBI
  - » Rapid and accurate determination of infection
  - » Test to predict progression to active TB

# Genome of *M. tuberculosis*

